

Irradiation device for therapeutic and cosmetic purposes

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The invention relates to an irradiation device for therapeutic and cosmetic purposes.

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Primary T cell mediated skin disorders, such as for example atopic dermatitis (neurodermatitis), cutaneous T cell lymphoma, alopecia areata, lichen ruber and psoriasis are based on a skin infiltration of activated T lymphocytes of the body itself. Ever more newborn infants and children are being affected in particular by neurodermatitis. This disorder is a considerable burden both physiologically and psychologically, on account of the inflamed body parts and the associated itching.

The known therapies for the treatment of neurodermatitis can be substantially divided into two classes, namely chemotherapy and UVA1 or UVB phototherapy.

In the case of chemotherapy, the current gold standard in the treatment of atopic dermatitis is glucocorticoid therapy. This therapy causes in some cases severe side effects both for systemic and for topical applications. Alternative methods for treating neurodermatitis include therapy using strong immunomodulating drugs, such as for example FK 506 or Cyclosporin A; there is as yet no experience of the long-term consequences of these drugs.

UVA1 phototherapy has proven effective in the treatment of acute cases of neurodermatitis, urticaria pigmentosa and localized dermatosclerosis. Currently, two types of apparatus are available for Meffert UVA1 therapy and Krutmann UVA1 therapy. Meffert UVA1 therapy operates on a broadband basis between 340 and 500 nm, while Krutmann UVA therapy operates at 340 - 400 nm.

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A very good overview of the prior art in the field of UVA1 therapy is provided by "Stellung zur Qualitätssicherung in der UVA 1-Phototherapie, Fassung der Untergruppe Foto-(Chemo)Therapie und -Diagnostik der Subkommission physikalische Verfahren in der Dermatologie, May 1998" [Position concerning quality assurance in UVA1 phototherapy, version from the photo(chemo)therapy and diagnostics of the subcommittee on physical processes in dermatology, May 1998], and by the "Richtlinien zur Qualitätssicherung in der Foto-(Chemo)Therapie und Diagnostik" [Guidelines on quality assurance in photo(chemo)therapy and diagnostics], published in "Krutmann, S., Hönigsmann, H.: Handbuch der Dermatologischen Phototherapie und -Diagnostik, Springer-Verlag, Heidelberg, pp. 392-395". These articles cite premature skin aging and carcinogenicity as long-term risks. In view of these facts, these articles explicitly state that the use of medium and high doses of UVA1 is not recommended for children. However, this rules out the largest group affected by neurodermatitis.

Furthermore, it is known that acne, which is a skin disorder which, unlike neurodermatitis, is caused by the growth of bacteria in blocked follicles of regions of the skin which are rich in sebaceous glands together with keratosis, can be treated with blue light in the range from 400 - 440 nm without significant proportions of UVA, but success has been limited. In this context, reference is made to the specialist article "V. Sigurdsson et al., Phototherapy of Acne Vulgaris with visible Light, Dermatology 1997; 194; Vol. 3. 256-260" which includes further literature references. This form of therapy started by using red fluorescence on acne follicles as part of the dermatological examination, using a woodlamp. The source determined for the fluorescence was the storage of large quantities of porphyrins in the propion bacterium acne (Mc Ginley et al., Facial follicular porphyrin fluorescence. Correlation with age and density of propionibacterium acnes, Br. J. Dermatol Vol. 102., Section 3, 437-441, 1980). Since the principal absorption (Soret band) of porphyrins is around 420 nm, it was obvious for Meffert et al. to treat bacteria-containing acne follicles with blue light.

The longest-wave absorption band of porphyrins is 630 nm with a penetration depth of 4 mm, which is most favorable for photodynamic follicle treatment

and is used for this purpose.

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Therefore, the invention is based on the technical problem of providing an irradiation device for treating primary T cell mediated skin disorders which has fewer side effects and in particular is also suitable for treating children.

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The solution to the technical object emerges from the features of patent claim 1. The surprising activity of the radiation on the T cells in the range from 400 - 440 nm has made it possible to create an irradiation device for the treatment of primary T cell mediated skin disorders which on the one hand makes it possible to treat skin disorders which it has scarcely been possible to treat previously, such as lichen ruber, and on the other hand, since the carcinogenicity is lower by powers of 10 compared to UVA, also allows children to be treated. Its efficacy has already been impressively confirmed in clinical trials. In these trials, the test subjects were treated with irradiation doses of between 10 and 200 joules, a preferred irradiation dose being 50 J in the wavelength range from 400 - 440 nm. Therefore, a further surprising effect is that a therapeutic effect is established even at 8% compared to the irradiation doses which have previously been prescribed. Consequently, it is possible to achieve lower irradiances, on the one hand, and shorter treatment times, on the other hand. Furthermore, it has been found that, unlike the 15 appointments which were previously required, even 3-5 days of treatment are sufficient, and according to information given by the patients a noticeable improvement occurred even after the first treatment. The area of the patient which is to be irradiated is at a distance of between 0.2 and 3 m from the irradiation device.

Since patient-specific thresholds for the irradiances for the therapeutic action of blue light cannot be ruled out, presumably on account of the different levels of melanin and/or antioxidants of the skin, an irradiance of greater than 20 mW/cm² for the wavelength range between 400 - 440 nm is preferably selected.

In general terms, however, in order to shorten treatment times it is attempted to use the highest possible irradiance in the wavelength range from 400 - 440 nm. In this context, tests have already been carried out using irradiances of greater than 60 mW/cm² and greater than 100 mW/cm². Conversely, it is attempted to ensure that the irradiances of the other wavelengths are suppressed as far as possible. Currently, gallium plasma radiators, which usually have an intensity ratio 400 - 440 nm:UVA:UVB of 100:20:0.5, are being used.

With the gallium plasma radiators used, the irradiance in the wavelength range from 300-400 nm is caused substantially by the spectral lines at 313 nm and 364 nm, the irradiance in the region of 313 nm being less than 0.5% compared to the irradiance in the wavelength range 400 - 440 nm.

By active filtering measures, it is possible to shift the ratio of the intensities, so that an irradiation device which is currently in operation has an irradiance of 58 mW/cm² in the wavelength range from 400 - 440 nm, an irradiance of 3 mW/cm² in the UVA range and an irradiance of 140 μW/cm² in the UVB range, corresponding to an intensity ratio of 100:5.2:0.25.

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With an administered radiation dose of 50 J in the wavelength range from 400 - 440 nm, the radiation dose in the UVB range fluctuated between 25 - 150 mJ. Despite these fluctuation bands, the UVB doses administered as a result lie considerably below the radiation doses from conventional UVB therapeutic techniques, which use starting doses of 200 mJ and increase to 800 mJ over the course of several weeks of treatment. The same applies, to a much greater extent, for the UVA ranges around 364 nm. However, it is impossible to rule out the possibility of small proportions of the UVB range around 313 nm having a synergistic effect on therapy in the wavelength range from 400 - 440 nm. This is currently the subject of further clinical trials, in which the effect and, if appropriate, thresholds for the irradiance and/or

radiation dose for the 313 nm wavelength are to be determined. The same applies in a corresponding way to the UVA elements, although a synergistic effect can most likely be ruled out in this case.

Furthermore, surprisingly the test subjects acquired a lasting tan, so that the irradiation device can also be used for cosmetic purposes, and in this case too can replace the known UV appliances which have problems in terms of the risk of skin cancer. Further advantageous configurations of the invention will emerge from the subclaims.

In a preferred embodiment, the optical radiation source of the irradiation device is designed as at least one mercury low-pressure discharge lamp, preferably with $\text{Sr}_2\text{P}_2\text{O}_7:\text{Eu}$ or $(\text{SrMg})_2\text{P}_2\text{O}_7:\text{Eu}$ phosphor used as the phosphor material. With these lamps, it is possible to achieve irradiances of greater than 50 mW/cm^2 even at a distance of 50 cm. By suitable focusing of the radiation emitted from the optical radiation sources onto the area being irradiated, it is possible to increase the effective irradiance still further, and this in principle also applies to the optical radiation sources described below.

In a further preferred embodiment, the optical radiation source is designed as a mercury high-pressure discharge lamp with metal halide additives gallium indium iodide and/or gallium iodide, the weight ratio between the mercury and the metal halide additives being 10-100. To increase efficacy, the quartz bulb, in the region of the electrodes, is made partially reflective using zirconium oxide.

To suppress the radiation components in the UVB range which are emitted on account of the mercury, the radiation device is assigned a UVB filter, which in the most simple case comprises a pane of glass. The UVB filter is preferably designed as a casing tube, which is arranged around the optical radiation source, and the region between casing tube and quartz bulb

is evacuated to a gas pressure of 10-500 torr. UV-opaque transparent plastics are preferably used to suppress the UVA components, these plastics preferably being in the form of sheets and, in addition to the UVA range, also filtering out the UVB range. By suitable doping of the plastics, it is possible to change their filtering capacity considerably, so that different intensity distributions can be established. This is of great interest in particular if it should emerge that certain UVB and/or UVA components or intensities reinforce a therapeutic effect.

In a further preferred embodiment, the optical radiation source is designed as an electrode-free mercury high-pressure discharge lamp, with the result that then the metal halides gallium chloride and/or gallium bromide which are preferred on account of their relatively high vapor pressure are predominantly used as dopants. The electromagnetic energy for the discharge is then introduced, by means of a magnetron with associated antenna, into a resonator which is formed by a metallic shield.

Furthermore, an IR filter is preferably provided, in order to suppress the undesirable thermal radiation. In order at the same time to ensure good dissipation of heat from the IR filter, a cooling unit with liquid cooling is assigned to the optical radiation sources, the liquid being in the form of an IR filter. The cooling unit preferably comprises two radiation cooler mounts with integrated inlets and outlets between which a transparent casing tube is arranged. The advantage of this arrangement is that the radiation cooler mounts are releasably connected to the optical radiation source, allowing them to be re-used in the event of defective optical radiation sources. Suitable coolants are in particular water and, for the electrode-free high-pressure lamp, silicone oil. Silicone oil has a large number of further advantages. In addition to a large stable temperature range, cooling to 4°C is possible. Silicone oil exhibits low absorption of microwave energy and at the same time acts as an IR filter.

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The invention is explained in more detail below with reference to a preferred exemplary embodiment. In the drawing:

- FIG. 1*
Fig. 1 shows a cross section through a mercury high-pressure discharge lamp,
Fig. 2 shows a cross section through a mercury high-pressure discharge lamp with integrated water cooling,
Fig. 3 shows vapor pressure curves of gallium and gallium halides,
Fig. 4 shows a cross section through an electrode-free high-pressure discharge lamp with cooling unit and a magnetron,
Fig. 5 shows a cross section through an electrode-free high-pressure discharge lamp with cooling unit and two magnetrons,
Fig. 6 shows a spectrum of a gallium plasma radiator,
Fig. 7 shows a spectrum of a high-pressure discharge lamp with a mercury:gallium iodide weight ratio of 44,
Fig. 8 shows a spectrum of a high-pressure discharge lamp with a mercury:gallium iodide weight ratio of 22,
Fig. 9 shows a spectrum of a high-pressure discharge lamp with a mercury:gallium iodide weight ratio of 8.8,
Fig. 10 shows a spectrum of a known gallium indium effect light,
Fig. 11 shows a diagrammatic cross-sectional illustration of an entire-body irradiation device, and
Fig. 12 shows a diagrammatic cross section through an irradiation arrangement with a high-power plasma radiator.

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The optical radiation source of the irradiation device for the treatment of primary T cell mediated skin disorders may be designed as either a low-pressure discharge lamp or a high-pressure discharge lamp. As explained in more detail below, however, a mercury high-pressure discharge lamp 1 in the spectrum has a few advantages over the known low-pressure discharge lamps for the spectral region which is of interest.

The mercury high-pressure discharge lamp 1 comprises a quartz bulb 2, in which two electrodes 3 are arranged. Electrical connection lines 4 for the supply of voltage are connected to the electrodes 3 and

lead to a threaded holder 5. A casing tube 6, which is closed at one end and at its other end is connected in a hermetically sealed manner to the threaded holder 5, is arranged around the quartz bulb 2. The space between casing tube 6 and quartz bulb 2 is evacuated to a gas pressure of 10-500 torr. The quartz bulb 2 contains mercury, argon and a metal halide additive, such as for example gallium iodide and/or gallium indium iodide, which preferably emits in the wavelength range from 400 - 440 nm. The irradiance and the spectra are dealt with in more detail below. The weight ratio of mercury to the metal halide additives is 10-100. In the output region of 400 W, a mixing ratio of 1-5 mg of metal halide additive to 44 mg of mercury is preferably used. Furthermore, the quartz bulb 2 has been made partially reflective in the region 8 of the electrodes 3 by means of zirconium oxide, in order to increase the temperature in the space of the quartz bulb 2 which is close to the electrodes. The casing tube 6 substantially has two functions. Firstly, it serves as a UVB filter, in order to reduce this undesired spectral component as far as possible. Secondly, the casing tube 6 serves for thermal insulation, since the surface of the quartz bulb 2 becomes very hot during operation. A further advantage of the casing tube 6 is that it protects the actual high-pressure discharge lamp from external temperature changes.

Fig. 2 shows a cross section through the mercury high-pressure discharge lamp 1 as shown in Fig. 1 with an integrated coolant unit. The coolant unit comprises a first radiation cooler mount 9 and a second radiation cooler mount 10 and a transparent casing tube 11. An inlet 12 and an outlet 13 are integrated into the two radiation cooler mounts 9, 10, and a flexible tube can be connected to the inlet and outlet. The first radiation cooler mount 9 is simply pushed onto the threaded holder 5. The transparent casing tube 11 is then pushed into the radiation cooler mount 9 and is closed off, on the opposite side from the threaded holder 5, by the second radiation cooler mount 10. A hermetically sealed circuit for the coolant

17 is formed between the inlet 12 and the outlet 13 by means of O-shaped sealing rings 14, 15, 16. In the simplest case, the coolant may be water. In this case, the coolant 17 serves predominantly to dissipate the heat which is produced at the evacuated casing tube 6, in order to keep the latter at a temperature of 40-60°C.

Since the penetration depth of blue light is limited, and both for disorders of the lower levels of the skin and skin appendages, such as the hair roots, and in the case of thickened skin caused by inflammation, as in psoriasis and dermatosclerosis, the radiation has to penetrate to a very great depth, it is advantageous to use an irradiation device in which the circulating coolant 17 is significantly cooler than the skin temperature. In this case, the cooled casing tube 11 can be placed directly onto the affected skin, in which case irradiances of the order of magnitude of approx. 1-2 W/cm² can be applied if the electrical connected power is 1000 W, since higher irradiances lead to a shorter treatment time. On account of the high tissue absorption of blue light, very high levels of heat are evolved in the upper tissue layers, and without this cooling to, for example, 4°C, this would otherwise lead to burning. By means of this cooling, the depth of action limited by a threshold dose can be extended to several millimeters and therefore into the region of the follicles. In the case of electrode lamps, a preferred coolant 17 is water. At the same time, the coolant 17 serves as an IR absorber.

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In addition, the casing tube 6 may be coated, on its inner side, with the phosphors which are known from low-pressure discharge lamps, in order in this way to transform additional components of the UVC radiation emitted by mercury into the wavelength range of 400 - 440 nm which is of interest. Since the phosphor itself has only low absorption in the range from 400 - 440 nm, it is in this way possible to effectively increase the emission in this wavelength range. A precondition for the use of blue phosphors in the evacuated casing tube, which may be filled with inert gas, is that the phosphor be cooled. Under normal operating conditions without cooling, the casing tube reaches up to 600°C. However, the efficiency of the blue

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phosphors drops greatly at temperatures above 100°C, so that they can only usefully be employed if the temperature is controlled at below 100°C, as can be achieved by means of the coolant unit described above. By using phosphors in combination with other dopants which preferably emit in the UV range in the quartz burner, it is possible to further increase the efficiency of the optical radiation source. Halide compounds of the metals selenium, antimony, zinc and cadmium are suitable for this purpose.

Fig. 3 shows the vapor pressure curves in torr plotted against the absolute temperature for the pure metal gallium and its halide salts gallium iodide, gallium chloride and gallium bromide. At the permissible wall temperatures without liquid cooling, pure gallium is inferior to the halides by several orders of magnitude, so that an efficient discharge with gallium can only be achieved at extremely high wall temperatures, which in turn requires greater cooling using, for example, silicone oil. Of the gallium halides illustrated, gallium iodide has the lowest vapor pressure. In this respect, gallium bromide is better by orders of magnitude. However, these bromides or chlorides are so aggressive that they would quickly destroy the electrodes 3 in the exemplary embodiments shown in Figs. 1 and 2.

Therefore, an irradiation device without electrodes 3, as illustrated in Fig. 4, is preferred when using gallium bromides or chlorides. The irradiation device 1 comprises a quartz bulb 2, in which the gallium or gallium halides are dispersed. The cooling unit which has already been described is arranged around the quartz bulb. A magnetron 18 with associated antenna 19 is arranged on at least one end face of a radiation cooler mount 9. Furthermore, a metallic shield 20, which forms a resonator for the electromagnetic waves emitted from the antenna 19, is arranged around the cooling unit. In this arrangement, it is not possible to use water as coolant 17, since water would excessively absorb the electromagnetic waves of the magnetron 18,

so that in this case the coolant used is preferably silicone oil.

With service lives of 10,000 - 20,000 hours and a better efficiency, electrode-free lamps have advantages over conventional light sources with electrodes 3. However, the emission from these lamps is influenced by temperature differences inside the lamp. If parts of the quartz bulb 2 (plasma ampule) are not heated uniformly, dark bands are formed, caused by self-absorption of the plasma. The temperature differences within the plasma source are often the result of an uneven field distribution of the microwave energy in the resonator. The result is an uneven discharge and a deterioration in the lamp output. In a preferred embodiment, the electromagnetic field distribution is controlled by means of a resonant cylinder which supports the E_{01} mode. In this case, the field distribution is such that the highest value of the electrical field is in the resonator axis and the electric field vector points in the radial direction. The field strength drops toward the conducting walls of the resonator, before disappearing at the conducting surface of the cylindrical shield 20. The power required is dependent on the plasma density which can be achieved. The plasma is concentrated in the center of the discharge vessel. With a coaxial orientation, the entire cylindrical shell of the quartz bulb 2 is situated in the region of the same field strength, so that there is no possibility of irregularities in this respect. For the E_{01} mode and the preferred excitation frequency of 2450 MHz, the resonant waveguide has a diameter of 9.37 cm. Under these conditions, the resonator can be of any length without the E_{01} resonance condition changing, with the result that in this way the resonator can easily be adapted to different powers by changing the length.

A further advantage of the E_{01} mode is that the symmetry means that electromagnetic energy can be introduced from two sides, as shown in Fig. 5,

which is important in particular for relatively great lengths of the quartz bulb 2. On account of the standing wave, only the diameter of the waveguide needs to be accurately observed. The distance between the two magnetrons 18 is not critical in relative terms. It should merely be ensured that the energy absorption in the plasma is sufficiently high for it to be impossible for any unattenuated waves to impinge upon the other magnetron 18, since this could cause its destruction.

As has already been stated, water cannot be used as coolant. Therefore, silicone oils, such as for example dimethyl polysiloxane are preferably used, having only a low microwave absorption of less than 0.2 W/cm per kilowatt of power. Silicone oil is transparent in the visible range and absorbs a significant IR component in the wavelength range of greater than 1 μm . Consequently, it is either possible to dispense with separate IR filters altogether or for such filters to be of less critical dimensions. Furthermore, dimethyl polysiloxane can be used over a wide temperature range of -70°C - 250°C . With this arrangement, it is possible to introduce up to 300 W/cm² of plasma without the quartz bulb 2 beginning to melt. Compared to the conventional air cooling of a plasma source, the noise which otherwise occurs with a high air flow is eliminated, which is psychologically more pleasant for the patient.

If the silicone oil cooling were to be dispensed with in the electrode-free system, it is possible to use a rotating plasma quartz ball which, for example, is arranged on a shaft and, during rotation in an E_{111} or E_{112} mode resonator, on average results in a uniform field distribution. Furthermore, the effective surface area for convection cooling is increased as a result. In this case, the ball rotation preferably takes place in two planes, so that on average complete field mixing is achieved. What is known as tumbling rotation, i.e. during rotation about the z axis the rod itself rotates about the lateral surface of a cone, represents an alternative which is technically simpler to implement.

Fig. 6 illustrates a spectrum of a typical gallium/mercury plasma radiator. The irradiance in the wavelength range between 300 - 400 nm is substantially determined by a peak at 364 nm and a peak at 313 nm, the former representing the UVA component and the latter representing the UVB component. These peaks represent typical spectral regions of mercury. The extent of the peaks fluctuates considerably with manufacturing tolerances, but as a good approximation the peak of the UVA component is less than 20% and the peak of the UVB component less than 0.5% of the irradiance in the wavelength range between 400 and 440 nm. On account of the low absolute irradiances in the UVA and UVB ranges, these ranges are not illustrated in the following spectra.

Figs. 7-10 show various spectra for different dopants, the irradiance in mW/cm^2 per 0.5 nm at a distance of 50 cm being plotted on the Y axis. The spectra illustrated show that for a mercury to gallium iodide weight ratio of 8.8, the emission in the spectral range between 400 - 440 nm decreases considerably. At the weight ratios 22 or 44, the yield in the spectral region which is of interest is significantly better. It is possible to further increase the emission in the range between 400 - 440 nm by adding indium iodide in a mercury/indium iodide ratio of 20-200. With the aid of the addition of small quantities of indium iodide, it is possible to increase the indium emission in the region of 405 nm without the blue emission in the region of 500 nm having an adverse effect on the energy yield in the spectral region between 400 - 440 nm which is of interest.

Fig. 11 diagrammatically depicts an entire-body irradiation device for a patient 21. For this device, a multiplicity of the optical radiation sources are arranged in an array, each optical radiation source being assigned a parabolic reflector 22. When using the cooling units described, these units can be connected to one another in meandering form. Alternatively, however, it is possible for only individual cooling units of the radiation sources to be combined, so that in this case

a plurality of cooling circuits with pumps are used. Preferably, the upper and lower parabolic reflectors 22 and the side walls are tilted upward or downward by approx. 5°, in order to obtain a more uniform irradiation power over the irradiated area. For a radiator length of 190 cm and a reflector aperture angle of 8°, the optimum radiation plane results at a distance of 45 - 50 cm. On account of the higher irradiation powers, the space between the irradiation arrangement and the patient is preferably cooled by circulating air conditioning.

Fig. 12 shows a further preferred embodiment of the irradiation device 1, in cross section. The irradiation device 1 comprises a gallium plasma radiator 20 with a quartz tube 21. In this case, the quartz tube 21 has a diameter of, for example, approx. 20 mm. The quartz tube 21 is preferably formed from UVC-absorbent quartz, in order to prevent the formation of ozone. A first casing tube 22 is arranged around the quartz tube 21, the casing tube consisting, for example, of Duran glass. The casing tube 22 is at a distance, for example, of 20 mm from the quartz tube 21 and is designed with a wall thickness of approx. 3 mm. Air is situated between the quartz tube 21 and the casing tube 22. A second, outer casing tube 23 is arranged around the first casing tube 22 and likewise preferably consists of Duran glass and has a wall thickness of 3 mm, the distance between the first casing tube 22 and the second casing tube 23 being approximately 10 mm. Water is situated between the two casing tubes 22, 23, and the radiation cooler mounts of the previous exemplary embodiments can be used to produce a closed cooling circuit. The advantage of this indirect cooling of the quartz tube 21 is that it prevents blackening caused by deposits of mercury compounds on the quartz tube 21 and the quartz tube 21 can be operated at optimum operating temperatures of between 600-900°C.